

# Uncoupling proteins in the failing human heart: friend or foe?

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### Author's reply

Jason Gardosi makes two points. The first is that doctors should be cautious about applying our results indiscriminately, because they might not be generalisable to the whole population of babies for whom early delivery is considered. Doctors who are faced with babies who they believe are less sick than those recruited to GRIT should obviously delay delivery. Equally, those treating babies who they believe are more sick, might decide to ignore our results and deliver. Their decision should be based on the results of observational studies, which can provide guidance on timing delivery to prevent fetal death. These studies are, however, a poor guide to timing delivery with the aim of reducing brain damage. We believe, in this instance, the GRIT results are better.

Gardosi's second point is more controversial. He suggests that doctors might have preferentially recruited patients for whom they believed a delay was preferable, so the trial gave them the result they wanted. However, he provides no justification for his belief that doctors would prefer one outcome over the other. The argument that specialists in fetal medicine, much of whose clinical practice is devoted to delivering babies early in the hope that they can prevent death and brain damage, would have hoped for the opposite result is just as strong. Irrespective of personal preferences, however, such behaviour would have been unethical. Furthermore, even if recruitment had been biased, the internal validity of the trial would not have been affected—for babies of the same gestational ages and with the same Doppler waveforms as those studied, the GRIT results are valid.

I declare that I have no conflict of interest.

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### Uncoupling proteins in the failing human heart: friend or foe?

Concentrations of circulating free fatty acids are increased in patients with heart disease and are inversely correlated with myocardial phosphocreatine-to-ATP ratio, an indicator of cardiac energy deficit. Andrew Murray and colleagues (Nov 13, p 1786)<sup>1</sup> report a positive relation between the concentration of circulating free fatty acids and the content of cardiac mitochondrial uncoupling proteins, and suggest this relation explains the energy deficit observed in the damaged heart. The presumption that is key to this statement is that uncoupling proteins indeed uncouple mitochondrial respiration.

Although data on the physiological function of uncoupling proteins in cardiac muscle is scarce, the few data available show similar results as in skeletal muscle, suggesting that the physiological function can be extrapolated from data obtained in skeletal muscle. As such, a rise in uncoupling proteins does not result in uncoupling of mitochondrial respiration from ATP production, as measured by post-depletion phosphocreatine resynthesis rate.<sup>2</sup>

There is compelling evidence that uncoupling proteins are involved in the outward translocation of fatty acid anions away from the mitochondrial matrix. When not all fatty acids can enter the mitochondria via carnitine-palmitoyl-transferase as oxidisable fatty acylCoA esters, the excess enter the mitochondrial matrix via a flip-flop mechanism in their unesterified (non-oxidisable) form where they become deprotonated. The resultant fatty acid anions cannot be oxidised nor leave the matrix due to the proton gradient and are therefore stuck in the matrix where they are harmful to the mitochondria.

Uncoupling proteins can act as outward transporters of these fatty acids, thereby protecting mitochondria in

conditions characterised by an oversupply of fatty acids.<sup>3</sup> In line with this function, uncoupling protein content inversely relates to oxidative capacity. Hence, concentrations of uncoupling protein are 14-fold lower in cardiac muscle than in glycolytic muscle.

Increasing the fat load to the mitochondria by consumption of a high fat diet upregulates uncoupling protein content profoundly in cardiac muscle.<sup>4</sup> Considering uncoupling protein as a fatty acid anion exporter, the positive association between plasma free fatty acid concentrations and cardiac uncoupling protein content<sup>1</sup> should be considered a beneficial—rather than an unfavourable—adaptive response, attempting to protect the damaged heart from lipotoxicity. In this context, inhibition of fat oxidation, which has been proposed as a treatment for heart disease, would result in upregulation not downregulation of concentrations of uncoupling proteins.<sup>5</sup> Again, this notion suggests that increased uncoupling protein content is beneficial for the damaged human heart.

Given that uncoupling proteins are unlikely to be responsible for the energy deficit observed in the damaged heart, the ideal treatment should maintain or augment cardiac uncoupling protein concentrations, while reducing the fatty acid load to the heart to prevent lipotoxicity. Finally, it is noteworthy that high fatty acid concentrations might be able to uncouple mitochondrial respiration, irrespective of uncoupling proteins, and thereby contribute to an energy deficit.

We declare that we have no conflict of interest.

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## Uses of Error: diagnosis, detection, and disclosure

We have been reading the Uses of Error in *The Lancet* for the unique insight they provide into what being a doctor is like. The accounts are often poignant and draw attention to how errors arise throughout a doctor's career and are long remembered.

149 patients have been described in the 107 essays published between 2001 and 2003, mostly from internal medicine (109 of 149 [73%])—18 additional Uses of Error are not discussed here because they describe multiple patients or contain general comments on error. The most frequent error type among the 107 essays assessed was associated with diagnosis (78 of 149 [52%]) usually attributed to misjudgment, a finding consistent with other voluntary reports.<sup>1,2</sup> In everyday life, however, slips and lapses—where the intention was correct but the execution went astray—are more common.<sup>3</sup> Why, therefore, is there such an emphasis on diagnostic errors?

Errors in diagnosis are more likely to result in a poor outcome.<sup>4,5</sup> Doctors might tolerate errors but not poor patient outcomes. Medical training focuses on making the correct diagno-

sis, and diagnostic errors undermine the notion of self. Furthermore, others view diagnostic errors negatively and are more likely to consider them negligent than skill-based errors and complications.<sup>4,5</sup> Finally, the system does not respond kindly to errors of diagnosis. An intention error is less likely to be detected and corrected than a slip or a lapse.<sup>3</sup> The culture of health care does little to enhance this process.

The reasons doctors give for diagnostic errors provide some insight into the cognitive processes. Diagnostic errors that arose early in the doctor's career were attributed to a lack of knowledge and experience, resulting in poor planning and an error of intention. During the consultant years, however, there were short cuts and often the doctor was working alone in the clinic. In these situations the consultants had the knowledge, but either lapsed or violated their own rules of practice. Strategies to reduce errors and to increase their detection hence need to be tailored to the context.

18 cases describe detection of an error before the patient was harmed. Apart from serendipity, three mechanisms for detection were described: (i) a second person—eg, nurse, technician, other doctor, mother—became involved who made the diagnosis, initiated an action, or made a comment that led to the correction; (ii) the doctor sensed that something was odd; and (iii) a back-up system detected the error (insulin overdose). Since there will never be a system free from errors, research focused on detection and mitigation of mistakes is needed.

Finally, the regular appearance of Uses of Error is contrary to public opinion that doctors wish to operate in a secret society. Many authors expressed a wish to have spoken about their errors earlier, but the mechanisms did not exist. The Uses of Error section is one mechanism but we need more.

We declare that we have no conflict of interest.

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## Department of Error

Hansmann G. Neonatal resuscitation on air: it is time to turn down the oxygen tanks.

*Lancet* 2004; **364**: 1293–94—In this Comment (Oct 9), there should be no question mark at the end of the title. The first sentence should read: "Participants of the Guidelines 2000 Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care<sup>1</sup> ...". The first sentence of paragraph three should read: "This conclusion is supported by another meta-analysis<sup>10</sup> on the data from five randomised or quasi-randomised studies.<sup>4,7–9,11"</sup>